Oxygen Uptake, Ventilation, and Symptoms During Low-Frequency Versus High-Frequency NMES in COPD: A Pilot Study.

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COPD

Oxygen Uptake, Ventilation, and Symptoms During Low-Frequency Versus High-Frequency NMES in COPD: A Pilot Study

Maurice J. H. Sillen · Emiel F. M. Wouters · Frits M. E. Franssen · Kenneth Meijer · Koen H. P. Stakenborg · Martijn A. Spruit

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Abstract Transcutaneous neuromuscular electrical stimulation (NMES) involves the application of an electrical current through electrodes placed on the skin over the targeted muscles. During high-frequency NMES (HF-NMES), oxygen uptake, minute ventilation, and the degree of symptom perception (dyspnea and fatigue) have been shown to be acceptable in chronic obstructive pulmonary disease (COPD). Currently, oxygen uptake and ventilation load have never been assessed during low-frequency NMES (LF-NMES) of the lower-limb muscles. The purpose of this study was to compare prospectively oxygen uptake, ventilation, and symptom perception during a single session of LF-NMES versus a single session of HF-NMES of quadriceps muscles in patients with COPD. In 17 COPD patients (mean $FEV_1 = 45\%$ predicted, mean body mass index = 26.2 kg/m^2), peak exercise capacity, functional exercise capacity, and the Medical Research Council dyspnea grade were evaluated. In addition, oxygen uptake, minute ventilation, heart rate, and Borg symptom scores were assessed during one session of LF-NMES (15 Hz) and one session of HF-NMES (75 Hz) and compared with peak values. Mean oxygen uptake (LF-NMES: 327 ml/min vs. HF-NMES: 315 ml/min), minute ventilation (LF-NMES: 14 L vs. HF-NMES: 15 L), and heart rate (LF-NMES: 86 BPM vs. HF-NMES: 83 BPM) were similar during both NMES frequencies. Patients used a relatively low proportion of their peak aerobic capacity during both NMES sessions (LF-NMES: 34% vs. HF-NMES: 33%; $P = 0.397$). In addition, symptom Borg scores for dyspnea and leg fatigue were also comparable. Oxygen uptake, ventilation, and symptoms of dyspnea and fatigue were comparable and tolerable during LF-NMES and HF-NMES in patients with COPD. Therefore, LF-NMES and HF-NMES may both be suitable rehabilitative modalities to be used in severely dyspneic patients with lower-limb muscle dysfunction.

Keywords Chronic obstructive pulmonary disease · Neuromuscular electrical stimulation · Oxygen uptake · Ventilation

M. J. H. Sillen (✉) · F. M. E. Franssen · M. A. Spruit
Program Development Centre, Ciro+, Hornerheide 1, Horn, The Netherlands
e-mail: mauricesillen@ciro-horn.nl

E. F. M. Wouters
Ciro+, Horn, The Netherlands

E. F. M. Wouters
Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

K. Meijer
Department of Human Movement Science, School for Nutrition, Toxicology and Metabolism of Maastricht, University Medical Centre (MUMC+), Maastricht University, Maastricht, The Netherlands

K. H. P. Stakenborg
Department of Biometrics, Ciro+, Horn, The Netherlands

Abbreviations

BMI	Body mass index
BPM	Beats per minute
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
DL_{CO}	Diffusion capacity of the lung for carbon monoxide
FEV_1	Forced expiratory volume in 1 s
FFMI	Fat-free mass index

HF-NMES	High-frequency transcutaneous neuromuscular electrical stimulation
IQR	Interquartile range
LF-NMES	Low-frequency transcutaneous neuromuscular electrical stimulation
MRC	Medical Research Council dyspnea scale
MVV	Maximal voluntary ventilation ($MVV = 40*FEV_1$)
% MVV	Percentage maximal voluntary ventilation
6MWD	Distance achieved by the 6-min walking test
NMES	Transcutaneous neuromuscular electrical stimulation
Peak HR	Peak heart rate
Peak VE	Peak minute ventilation (in liters, L)
Peak VO_2	Peak oxygen uptake (in ml/min)
% pred	Percentage predicted value
VC max	Maximum vital capacity

Introduction

Lower-limb skeletal muscle dysfunction (e.g., quadriceps weakness and/or loss of quadriceps muscle endurance) is a common extrapulmonary manifestation of chronic obstructive pulmonary disease (COPD) [1–3] and contributes to a poor exercise performance, increased use of health care, and mortality in COPD patients [4–6]. Daily physical inactivity partially determines skeletal muscle dysfunction in COPD [7]. Therefore, these patients have a clear indication for pulmonary rehabilitation [8, 9].

Exercise-based rehabilitation programs are able to improve lower-limb muscle strength and endurance, functional exercise performance, and health status in patients with COPD [10, 11]. Exercise training programs typically consist of lower-limb endurance/interval training, resistance training, or a combination thereof [12, 13]. Unfortunately, the benefits of these lower-limb endurance exercises (e.g., treadmill walking and/or stationary ergometry cycling) may be limited in COPD patients due to exercise-induced dyspnea and ventilatory limitation during training [14]. Indeed, aerobic exercise training can result in high values of oxygen uptake and ventilation, which exact a relatively high claim on the peak aerobic capacity of patients with COPD [14]. Therefore, there is great interest in new and effective alternative rehabilitative modalities that do not evoke dyspnea, such as high-intensity resistance training and transcutaneous neuromuscular electrical stimulation (NMES) [14, 15].

NMES involves the application of an electrical current through electrodes placed on the skin over the targeted muscles, thereby depolarizing motor endplates and, in turn, inducing skeletal muscle contractions [16, 17]. In patients with chronic heart failure, low-frequency NMES (LF-NMES, <50 Hz) increased muscle endurance [18], whereas high-frequency NMES (HF-NMES, ≥50 Hz) increased muscle strength [19]. To date, it remains unknown which stimulation frequency leads to better gains in muscle strength and endurance and which stimulation protocol is optimal for patients with COPD. Indeed, the effects of LF-NMES are unknown in COPD. Nevertheless, due to the striking similarities in systemic factors that contribute to exercise intolerance in patients with COPD or chronic heart failure [20], a reduced fiber type I proportion [21], and loss of muscle endurance in COPD [1, 22], it seems reasonable to hypothesize that LF-NMES will also have positive effects on quadriceps muscle endurance and functional exercise capacity in COPD.

Recently, oxygen uptake, minute ventilation, and the degree of symptom perception (dyspnea and fatigue) have been shown to be acceptable during a single session of HF-NMES in patients with COPD [15]. During LF-NMES, the authors expect also a relatively low and acceptable oxygen uptake and ventilation, which is comparable to those during HF-NMES [15]. Currently, this has never been studied but seems a necessary step prior to a randomized controlled trial in which the effects of NMES (LF vs. HF) on lower-limb muscle dysfunction are assessed in COPD.

The purpose of this study was to compare prospectively oxygen uptake, ventilation, and symptom perception during a single session of LF-NMES and a single session of HF-NMES of the quadriceps muscles in patients with COPD. In addition, safety was assessed by monitoring adverse events.

Methods

Study Subjects

Seventeen patients (10 men) with clinically stable COPD [23] were recruited at the start of a comprehensive pulmonary rehabilitation program at Ciro+ in Horn (the Netherlands) [9]. Patients were considered ineligible to participate if they had neuromuscular disorders, metal implants in the lower limbs, a cardiac pacemaker, and/or an exacerbation of symptoms in the preceding 4 weeks. Patients with long-term oxygen therapy were excluded because of the methodology that is used to measure oxygen uptake and ventilation (e.g., Oxycon Mobile).

Study Design

This was a prospective, randomized crossover pilot study. The study protocol was approved by the Medical Ethical

Committee of the Maastricht University Medical Centre+ (MEC 09-3-004) and conformed to the principles outlined in the World Medical Association declaration of Helsinki which was revised in Seoul. Details of the trial were registered at www.trialregister.nl (NTR1834) before subject enrolment. All patients gave written informed consent to take part in the study.

Pulmonary function, body composition (whole-body dual-energy X-ray absorptiometry), peak cycling load, peak aerobic capacity, functional exercise capacity, quadriceps muscle strength, Borg symptom scores for dyspnea and fatigue, and the Medical Research Council dyspnea grade were determined at baseline as a routine part of entry into the pulmonary rehabilitation program [9, 24]. Coexisting morbidities were assessed using the Charlson comorbidity index (CCI) [25]. Moreover, all patients underwent a single session of LF-NMES and a single session of HF-NMES on two separate days within the same week, in random order. These sessions occurred during the first week of the rehabilitation program, 0–4 weeks after the baseline testing. Randomization was performed by means of a computer-generated randomization list.

Safety was assessed by monitoring adverse events. Adverse events were defined as changes in health or side-effects, such as pain and/or muscle cramps, that occurred in patients who participated in the study while receiving the treatment.

Methods

During both NMES sessions, continuous online calculations of breath-by-breath oxygen uptake (VO_2) and minute ventilation (V_E) were obtained using the Oxycon Mobile, a portable metabolic system (CareFusion, San Diego, CA, USA) (Fig. 1). After calibration, the face mask (Combitox, Dräger Safety, Lübeck, Germany) was carefully adjusted to the patient's face and checked for air leaks. Data were collected breath by breath and processed using JLAB ver. 5.20b software (CareFusion).

NMES Protocols

During both NMES sessions, bilateral electrical stimulation of the quadriceps muscles was applied using a portable electrical stimulator (Gymnex 4, GymnaUniphy N.V., Bilzen, Belgium). A total of eight electrodes were placed on the quadriceps femoris muscles (four on each leg): two on the vastus medialis, one on the rectus femoris muscle, and one on the vastus lateralis muscle (Fig. 1). Both stimulation protocols were preset in the devices. The stimulation protocol of LF-NMES consisted of a symmetrical biphasic square pulse at 15 Hz, a duty cycle of 8 s on and 2 s off, a pulse time of 390 μs during a session lasting 29 min. The stimulation protocol of the HF-NMES consisted of a symmetrical biphasic square pulse at 75 Hz, a duty cycle of 6 s on and 29 s off, a pulse time of 410 μs during a session lasting 21 min. During both sessions the intensity was increased to maximum individual toleration. The muscle contractions were visible and palpable. In addition, Borg symptom scores for dyspnea and leg fatigue were obtained before and after both NMES sessions [26].

Fig. 1 Measurement of oxygen uptake and minute ventilation during a session of bilateral NMES of the quadriceps muscles in a male patient with COPD

Statistical Analysis

All statistical analyses were performed using SPSS for Windows ver. 17.0.1 (SPSS, Inc., Chicago, IL, USA). Continuous data were tested for normality and presented as mean and standard deviation or as median and interquartile range (IQR). In addition, two-tailed paired *t* tests were used for within-group comparisons. A priori, the level of statistical significance was set at $P \leq 0.05$.

Results

Characteristics

The baseline characteristics of the patients are given in Table 1. On average, patients had moderate to severe COPD and the lungs had poor diffusing capacity for carbon monoxide (Table 1). Most patients were severely dyspneic, reporting on the MRC dyspnea scale that they had to stop for breath after walking 100 yards (91.4 m) or after a few minutes on the level. Moreover, patients had explicit quadriceps weakness (mean ± SD = 55 ± 12% predicted [27]), as well as poor functional and peak exercise performance, with a mean ± SD 6-min walk distance of 380 ± 98 m [28], VO_2 max and maximal workload during CPET of 986 ± 260 ml/min and 60 ± 21 W, respectively.

Table 1 Participant characteristics

Age (years)	67 ± 9
Body weight (kg)	72.7 ± 14.7
BMI (kg/m^2)	26.2 ± 4.5
FFMI (kg/m^2)	17.5 ± 2.4
FEV_1 (% predicted)	45 ± 16
FEV_1/VC max (%)	35 ± 8
DL_{CO} (% predicted)	57 ± 22
MRC dyspnea (grade)	4 ± 1
Peak torque quadriceps muscles (% predicted)	55 ± 12
6MWD (m)	380 ± 98
6MWD (% predicted)	63 ± 17
Peak load CPET (W)	60 ± 21
Peak load CPET (% predicted)	52 ± 26
Peak VO_2 CPET (ml/min)	986 ± 260
Peak VO_2 CPET (% predicted)	66 ± 30
Peak VCO_2 CPET (ml/min)	945 ± 281
Peak VE CPET (L)	38 ± 9
Peak VE CPET (% MVV)	93 ± 23
Peak HR CPET (BPM)	119 ± 15
Peak HR CPET (% predicted)	78 ± 8
Borg dyspnea CPET (points)	8 ± 2
Borg fatigue CPET (points)	6 ± 2

Data are presented as mean ± SD

BMI body mass index, *FFMI* fat-free mass index, *FEV_1* forced expiratory volume in 1 s, *VC max* maximum vital capacity, *DL_{CO}* diffusion capacity of the lung for carbon monoxide, *MRC* Medical Research Council dyspnea scale, *6MWD* distance achieved by the 6-min walking test, *peak load* maximum workload, *CPET* cardiopulmonary exercise test, *peak VO_2* peak oxygen uptake in ml/min, *peak VE* peak minute ventilation in liters, *peak HR* peak heart rate, *bpm* beats per minute, *% pred* percentage predicted value, *% MVV* percentage maximal voluntary ventilation

On average, patients were ventilatory limited at the end of the cardiopulmonary exercise test, with high Borg scores for dyspnea and fatigue (Table 1).

Significant comorbidities were present in 10 of 17 (59%) patients with COPD. Indeed, the median score on the Charlson comorbidity index was 2 (IQR = 1-2.5) points. These comorbidities included coronary heart disease ($n = 5$), diabetes ($n = 3$), nonmetastatic solid malignancy ($n = 2$), peripheral artery disease ($n = 2$), chronic heart failure ($n = 1$), transient ischemic attack ($n = 1$), Bechterew's disease ($n = 1$), and/or peptic ulcer ($n = 1$). The following pulmonary maintenance medications were used by 17 COPD patients who volunteered to participate: short-acting β_2 agonists ($n = 8$), short-acting anticholinergics ($n = 1$), short-acting combined bronchodilators ($n = 7$), long-acting β_2 agonists (LABA) ($n = 3$), long-acting anticholinergics ($n = 15$), inhaled glucocorticosteroids (alone or in combination with LABA) ($n = 16$), systemic glucocorticosteroids ($n = 2$), xanthine derivatives ($n = 3$), antioxidant agents ($n = 5$), and/or leukotriene modifiers ($n = 1$).

LF-NMES Versus HF-NMES

All patients were able to complete both NMES sessions. No differences in tolerating both frequencies were reported and no adverse events occurred during either training session.

The effects of LF-NMES and HF-NMES are compared in Table 2. Mean resting and peak oxygen uptake, minute ventilation, and heart rate were not significantly different between LF-NMES and HF-NMES sessions (Table 2). Indeed, patients used a relatively low proportion of their peak aerobic capacity, measured previously during a CPET, during both NMES sessions (LF-NMES, 34%; HF-NMES, 33%; $P = 0.386$). Also, Borg symptom scores for dyspnea and leg fatigue were comparable for both NMES types (Table 2).

Discussion

The present pilot study is the first to assess oxygen uptake, ventilation, and symptom perception during a session of LF-NMES and a session of HF-NMES. Both NMES frequencies appear to be safe and sustainable in dyspneic COPD patients with comorbidities. Moreover, oxygen uptake, ventilation, and Borg symptom scores for dyspnea and leg fatigue were relatively low and comparable between LF-NMES and HF-NMES.

HF-NMES is a relatively new exercise modality used in the rehabilitation of (severely) disabled patients with COPD [17, 29, 30]. For example, 4–6 weeks of HF-NMES to the quadriceps muscles resulted in improved muscle strength, exercise capacity, and disease-specific quality of life in COPD patients who had an abnormal baseline body composition or who were too dyspneic to leave their home for a hospital-based outpatient pulmonary rehabilitation program [31, 32]. Indeed, HF-NMES has even resulted in faster mobilization from bed to chair in bed-bound COPD patients requiring prolonged mechanical ventilation [33]. Therefore, it seems reasonable to conclude that HF-NMES is safe, feasible, and beneficial in patients with COPD [29]. Indeed, international guidelines recommend HF-NMES in patients with severe chronic respiratory disease with extreme skeletal muscle weakness or who are bed-bound [8].

To date, the effects of LF-NMES in COPD patients have not been studied. Nevertheless, based on the combination of severe dyspnea at rest and a clear loss of lower-limb muscle endurance [1], it may be worthwhile to assess the effects of LF-NMES on the ambulation muscles of patients with COPD. The present findings provide additional rationale to assess the effects of LF-NMES in patients with

Table 2 Low-frequency NMES versus high-frequency NMES in COPD

	Low-frequency NMES	High-frequency NMES	*P* value
Resting VO_2 (ml/min)	258 ± 65	238 ± 51	0.178
Peak VO_2 (ml/min)	327 ± 96	315 ± 84	0.538
Peak VO_2 (% peak VO_2 CPET)	34 ± 12	33 ± 12	0.386
Resting VE (l)	11 ± 2	11 ± 2	0.633
Peak VE (l)	14 ± 4	15 ± 4	0.582
Peak VE (% MVV)	36 ± 13	38 ± 15	0.249
Peak HR (BPM)	86 ± 13	83 ± 11	0.284
Peak HR (% CPET)	72 ± 13	71 ± 11	0.374
Borg dyspnoea (Points)	2 ± 1	2 ± 1	0.154
Borg fatigue (Points)	2 ± 2	2 ± 1	0.680

The data are presented as mean ± SD before and after a single session of low-frequency neuromuscular electrical stimulation (LF-NMES) versus high-frequency neuromuscular electrical stimulation (HF-NMES) in 17 COPD patients.

VO_2 oxygen uptake in ml/min, *% peak VO_2 CPET* oxygen uptake expressed as a proportion of the peak VO_2 obtained at the end of a symptom-limited cardiopulmonary exercise test, *peak VE* peak minute ventilation in l, *% MVV* percentage maximal voluntary ventilation (MVV = 40 × FEV_1)

COPD who are severely disabled by their dyspnea. In fact, mean peak oxygen uptake, ventilation, and heart rate were well below maximum values during a session of LF-NMES and comparable to the values during a session of HF-NMES (Table 2).

Oxygen uptake, ventilation, and symptoms during a session of HF-NMES in the present study corroborate previous results of our group [15]. Yet again, these findings show that COPD patients use a clearly lower proportion of their peak aerobic capacity during a session of NMES compared to a session of high-intensity lower-limb resistance training [15], treadmill walking, or stationary cycling [14]. Indeed, the biphasic current used during the HF-NMES and the LF-NMES was well tolerated by the patients (e.g., no drop out from the protocol and no adverse events) and led to acceptable levels of dyspnea and fatigue in COPD (Table 2).

This pilot study had some methodological limitations and selected patient characteristics that may limit the external validity and broad applicability of the present findings. Only patients without long-term oxygen therapy were eligible to participate due to the methodology used [14]. This study included a small number of COPD patients with a wide range of disease severity and different levels of physical function. Some of the participants may not be the typical patient who receives NMES in daily clinical practice. Indeed, NMES can be particularly useful for severely disabled patients with COPD [29].

Moreover, oxygen uptake and ventilation was evaluated during only a single session of LF-NMES and HF-NMES. Therefore, it is not possible to draw conclusions regarding the relative values of oxygen uptake and ventilation over longer periods of training or to identify subpopulations of patients who may benefit from either technique.

Session time, duty cycle, and pulse duration differed between both NMES protocols. This was due to the preset protocols of the commercially available NMES device. Nevertheless, the impact of these NMES features on the primary outcome (i.e., oxygen uptake) is expected to be nil.

Finally, magnetic stimulation can also be used as a nonvoluntary lower-limb muscle training method in patients with COPD [34]. However, magnetic stimulation is rather expensive and its clinical applicability in groups of COPD patients in clinical routine seems challenging.

In conclusion, oxygen uptake, ventilation, and symptom perception of dyspnea and leg fatigue were sustainably low and comparable during a single session of LF-NMES and HF-NMES in patients with COPD. These pilot findings provide an additional rationale to design randomized controlled trials to compare the effects of LF-NMES and HF-NMES on lower-limb dysfunction in (severely) disabled patients with COPD.

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Conflict of interest The authors have no conflicts of interest or financial ties to disclose.

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